THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Complete Specification, Abstract & Drawings of the extract of Patent Application No.568/MAS/2002, dated 29.07.2002 by Dr. Reddy's Laboratories Limited having its registered office at 7-1-27, Ameerpet, Hyderabad 500 016, Andhra Pradesh, India.

.....

.....**In witness thereof**

I have hereunto set my hand

Dated this the 19h day of February 2004

M. S. V

(M.S. VENKATARAMAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

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OVE MENT OF INDIA
na C plex, 6th Floor, Annex.II
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Received Rs 5000/- in Cash
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FORM 1

THE PATENTS ACT, 1970
APPLICATION FOR GRANT OF A PATENT (Section 5(2), 7and Rule 33A)

We, Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016 hereby declare

1. (a) that we are in possession of an invention titled "**Novel Crystalline Form-III of 2-butyl-4-chloro-1- [[2'-(1H- tetrazol-5-yl) [1,1'-biphenyl]-4-yl] methyl]-1H-imidazole-5-methanol potassium salt (Losartan Potassium)**"
   (b) that the complete specification relating to this invention is filed with this application.
   (c) that there is no lawful ground of objection to the grant of a patent to us.
2. further declare that the inventors for the said invention are **Satyanarayana Reddy Manne, Eswaraiah Sajja, Ravinder Reddy Koppera and Venkat Reddy Vajrala** All citizens & residents of India belonging to **Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad – 500 016, Andhra Pradesh.**
3. that we are the assignee of the true and first inventors
4. that our address for service in India is as follows;

   Dr. M. Satyanarayana Reddy,
   Vice President
   Dr. Reddy's Laboratories Limited
   7-1-27, Ameerpet
   Hyderabad, A.P., 500 016

5. following declaration was given by inventors.
   We, the true and first inventors for this invention declare that the applicant herein is our assignee.

Signed)_____
Satyanarayana Reddy Manne
H.No: 8-3-167/D/16,
Kalyan Nagar
Near AG Colony
Erragadda
Hyderabad- 500 038

Signed)_____
Eswaraiah Sajja
LIG 100,
Dharma Reddy Colony,
K.P.H.B Colony
Kukatpally
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29 JUL 2002 568 MAS 2002

ORIGINAL

Signed)_____

Ravinder Reddy Koppera
Plot.No. 211, Vasanthanagar,
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Signed)_____

Venkat Reddy Vajrala
E.W.S 1172/A
Near Bank of Maharastra
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Hyderabad –500 072.

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application

7. following are the attachments with the application
   (a) complete specification (---12- pages, in triplicate)
   (b) abstract of the invention (--01-- page, in triplicate)
   (c) drawings (--03- pages, in triplicate)
   (d) fee Rs. 5000.00 (five thousand rupees only) Cheque vide No.336260 dated July 17 th drawn on HDFC Bank, Lakdikapool, Hyderabad- 500 004.

We request that a patent may be granted to us for the said invention

Dated this 23rd day of July, 2002.

(Signed)_____

Dr. M. Satyanarayana Reddy,
Vice President
Dr. Reddy's Laboratories Limited.

To, The Controller of Patents
The Patents Office Branch, Chennai.

FORM-2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

(SECTION 10)

Novel Crystalline Form-III of 2-Butyl-4-chloro-1- [[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl] methyl]-1H-imidazole-5-methanol potassium salt

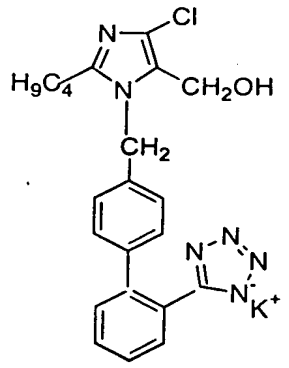
(Losartan potassium)

Dr. Reddy's Laboratories Limited,
An Indian Company having its registered office at
7-1-27, Ameerpet,
Hyderabad-500 016, A.P., India.

The following specification particularly describes the nature of this invention and the manner on which it is to be performed.

FIELD OF THE INVENTION

The present invention relates to the novel crystalline form of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl) [1,1'-biphenyl]-4-yl] methyl]-1H-imidazole-5-methanol potassium salt, generically referred as Losartan potassium. The present invention also relates to the process for the preparation of the novel crystalline form of Losartan potassium, which can be depicted as Formula (1).



Formula (1)

Losartan potassium is useful as angiotension II blockers. These compounds have activity in treating hypertension and congestive heart failures.

BACK GROUND OF THE INVENTION

USP 5,138,069 claims Losartan, its derivatives and pharmaceutically acceptable salts including potassium salt. The '069 patent also claims the composition and method of treatment using Losartan pharmaceutically acceptable salts and derivatives. The patent also discloses the process for the preparation of Losartan and its derivatives, which comprises deprotection of trityl Losartan with 3.4 N

hydrochloric acid to get the losartan base, which is then converted to its potassium salt by reacting with aqueous potassium hydroxide in isopropanol solution.

USP 5,608,075 discloses the polymorphic forms namely Form-I and Form-II of Losartan potassium and process for the preparation thereof. The process for the preparation of Form-I comprises treating the Losartan with potassium hydroxide solution followed by addition of resulting mass to the refluxing azeotropic mixture of cyclohexane and isopropanol, continued the distillation of solvent until the moisture content reaches <0.05% yielded the Form-I of Losartan potassium in white crystalline solid.

Further by heating the Form-I of Losartan potassium in a differential scanning calorimetric cell at a temperature of 255^{o}C in an open pan yielded the Form-II of Losartan potassium. Crystalline polymorphs Form-I and Form-II of Losartan potassium are differentiated by X-Ray diffraction, differential scanning calorimetry and infrared spectra.

The latest trend that has crept into the pharmaceutical industry is the studies on polymorphism in drugs and the difference in the activity of different polymorphic forms of a given drug. This has especially become very interesting after observing that many antibiotics, antibacterial, tranquillizers etc. exhibit polymorphism and some/one of the polymorphic forms of a given drug exhibit superior bioavailability and consequently show much higher activity compared to other polymorphs.

Hence, the present invention is directed to the crystalline forms of Losartan potassium. The Losartan potassium produced as per the process disclosed in USP

5,608,075 has resulted crystalline polymorphs Form-I, Form-II and further analyzed by X-ray diffractogram.

The crystalline compound thus obtained in the present invention is conveniently designated as .crystalline polymorph Form-III, herein after it is referred as crystalline Form-III of Losartan potassium.

The crystalline Form-III of Losartan potassium of the present invention is high melting solid with residual solvents within permissible limits as per ICH guidelines and may be very well suited for formulation applications.

The processes of the present invention are simple, non-hazardous and easily scalable for commercial production.

SUMMARY OF THE INVENTION

The present invention is directed to the novel crystalline Form-III of Losartan potassium. The present invention also relates to the process for the preparation of novel crystalline Form-III of Losartan potassium, which involves treating Trityl Losartan with aqueous solution of potassium hydroxide in an alcoholic solvent such as methanol resulted the desired product and was isolated from a mixture of toluene and methanol.

BRIEF DESCRIPTION OF ACCOMPANYING DRAWINGS

Fig. 1 is characteristic X-ray powder diffractogram of the present invention.

Fig.2 is characteristic Differential Scanning Colorimetry thermogram of the present invention.

Fig. 3 is characteristic Infrared spectral data of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the novel crystalline Form-III of Losartan potassium. The novel crystalline Form-III of the present invention is characterized by X-ray diffractogram, differential scanning colorimetric thermogram and Infrared spectral data.

The X-ray powder diffraction pattern of the novel crystalline Form-III was measured on a Bruker Axs, D8 Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source (Fig.1).

The novel crystalline Form-III of Losartan potassium has X-ray powder diffraction pattern essentially as shown in the Table-1. The X-ray powder diffraction pattern is expressed in terms of the 2 θ (degrees), and percentage of intensities (in %).

Table-1:

2-Theta (°)	**Intensity (I/I_O)**
7.154	100
13.911	29.9
20.728	23.4
24.904	22.0
24.192	21.1
19.293	16.1
8.042	14.6
7.583	14.4
16.043	13.6
17.194	13.3
28.908	12.5
29.474	11.9
26.088	11.5
21.576	11.5
15.267	11.1
18.483	11.0
17.794	10.1
13.233	7.60
19.571	7.20
30.614	6.80

The novel crystalline Form-III of Losartan potassium of the present invention was characterized by its X-Ray powder diffraction pattern substantially as depicted in Figure (1).

The present invention provides the Differential Scanning Calorimetry thermogram of the novel crystalline Form-III of Losartan potassium. The present inventive substance is measured on Schimadzu differential scanning colorimeter in a temperature range of 50-300^{O}C with a heating rate of 5^{O}C/minute and a nitrogen flow of 30ml/minute.

The Differential Scanning Calorimetry thermogram exhibits a major significant endo peak at 264.31°C and the relevant thermo gram is substantially as depicted in Figure (2).

The present invention also provides the Infrared spectral data of novel crystalline Form-III of Losartan potassium. The Infrared spectral data which was measured on Perkin-Elmer FT-IR instrument by KBr-transmission method with identified significant bands at about 1580, 1460, 1422, 1358, 1257, 1112, 1075, 999, 754, 668 cm^{-1} substantially as depicted in Figure (3).

The novel crystalline Form-III of present invention is having a melting range (capillary method) in the temperature of 254-260 °C.

Another aspect of the present invention is to provide a process for the preparation of novel crystalline Form-III of Losartan potassium, which comprises;

a) refluxing the reaction solution of 2-n-Butyl-4-chloro-1- [(2'-(1-triphenylmethyl-1H-tetrazole-5-yl)-1,1'-biphenyl-4-yl) methyl] 1H-imidazole-5-methanol (trityl Losartan) in a mixture of aqueous solution

of potassium hydroxide and C_1-C_4 straight or branched chain alcoholic solvents such as methanol, ethanol, isopropanol, n-butanol, iso-butanol and tertiary butanol, preferably methanol;

b) distilling off the solvent from the reaction solution of step (a);

c) cooling the reaction mass of step (b) to a temperature of 25-40^{o}C accompanied by addition of water;

d) filtering the reaction mass of step (c);

e) washing the filtrate obtained in step (d) with aromatic solvents such as benzene, xylene, toluene or ethyl benzene, preferably toluene;

f) separating the layers from reaction solution of step (e) and accompanied by distilling the water from aqueous layer;

g) azeotropic distillation of water traces from the reaction mass of step (f) using water immisible aromatic solvents such as benzene, xylene, toluene or ethyl benzene, preferably toluene;

h) dissolving the compound of step (g) in C_1-C_4 straight or branched chain alcoholic solvents such as methanol, ethanol, isopropanol, n-butanol, iso-butanol and tertiary butanol, preferably methanol;

i) optionally subjecting the reaction solution of step (h) with carbon;

j) optionally distilling the part of solvent from reaction solution of step (i) accompanied by cooling the resulting reaction mass to a temperature of 0-50^{o}C;

k) filtering the compound obtained in step (j) followed by drying the compound at temperature of 30-100^{O}C to afford the desired novel crystalline Form-III of Losartan potassium.

The present invention provides another process for the preparation of Losartan potassium, which comprises of;

a) heating the crystalline Form-I of Losartan potassium salt in water immisible aromatic solvents such as benzene, xylene, toluene or ethyl benzene, preferably toluene;

b) adding the C1-C4 straight or branched chain alcoholic solvents such as methanol, ethanol, isopropanol, n-butanol, iso-butanol and tertiary butanol, preferably methanol to the resulting reaction solution obtained in step (a);

c) distilling the part of solvent from the reaction solution of step (b) accompanied by cooling the reaction mass to a temperature of 10-50^{O}C, preferably 25-30^{O}C;

d) filtering the compound obtained in step (c) followed by drying the compound at a temperature of 30-100^{O}C to afford the desired novel crystalline Form-III of Losartan potassium.

Thus, the present invention provides novel crystalline Form-III of Losartan potassium.

The novel crystalline Form-III of Losartan potassium is high melting, free flowing solid and resulted in a non-solvated crystalline form. Hence, the present inventive substance is well suited for the pharmaceutical applications.

The processes of the present invention are simple, non-hazardous and easily scalable.

The following examples illustrate the invention but do not limit the scope of further invention.

Reference Example:

Preparation of Trityl Losartan:

To a mixture of 2-n-butyl-4-chloro-5-formyl imidazole (54 grams), tetrabutyl ammonium bromide (14 grams) in toluene (1000 ml) was added an aqueous solution of sodium hydroxide (15 grams in 700 ml water) and stirred the resulting reaction mixture for 20-30 minutes at a temperature of 30-35^{O}C. N-(triphenylmethyl)-5-[4'-(bromomethyl) biphenyl-2-yl] tetrazole) (170 grams) was added to the resulting reaction mixture and stirred for 33-35 hours. Then, the reaction completion was confirmed by TLC method. The organic layer was separated from the reaction mass and washed with dilute sodium hydroxide solution (40 ml), further with water (600 ml). Then sodium borohydride (4.0 grams) was added to the resulting organic layer, heated to a temperature of 40-45^{O}C, methanol (40 ml) was added and maintained for 11/2 –2 hours. The reaction mass was washed with water (3x200 ml), cooled to a temperature of 0-5^{O}C and stirred for 11/2-2 hours to separate the solid. Thus, the obtained solid was filtered and dried to afford the desired Trityl Losartan compound (140-145 grams).

Preparation of novel crystalline Form-III of Losartan potassium:

Example 1

2-n-Butyl-4-chloro-1- [(2'-(1-triphenylmethyl-1H-tetrazole-5-yl)-1,1'-biphenyl-4-yl) methyl] 1H-imidazole-5-methanol (Trityl Losartan) (125 grams, prepared as per reference example) in a mixture of aqueous potassium hydroxide solution (11g in 125 ml of water) and methanol (1250 ml) was refluxed till the reaction substantially completes. Then the solvent was distilled off from the reaction solution under vacuum. Water (375ml) was added to the residual mass, stirred for 30 minutes, filtered and washed with water (150 ml). Thus obtained filtrate was washed with toluene (2x110 ml) and separated the aqueous layer from the resulting bi-phase mixture. Water was distilled from aqueous layer and remaining water was removed azeotropically by the addition of toluene (350 ml) under reflux condition. Then methanol (100ml) and carbon (5.5 grams) were added to the resulting residue and stirred for 30 minutes for clear dissolution. The carbon was filtered off and washed with methanol (50 ml). The methanol was distilled off accompanied by cooling the reaction mass to a temperature of 20-25°C to separate the solid mass. The separated solid was filtered, washed with methanol (50 ml) and dried at a temperature of 80-90^{o}C to afford the crystalline Form-III of Losartan potassium. (Weight: 75.0 grams, 86.5 %)

Example 2:

Crystalline Form-I of Losartan Potassium (20.0 grams) was dissolved in toluene (160 ml) at a temperature of 70^{o}C. Methanol (30 ml) was added to the reaction solution and stirred for 10 minutes. The reaction solution concentrated under

vacuum to a minum value. The resulting residual mass was cooled to a temperature of 25-30^{O}C and stirred for 15-30 minutes. The solid was filtered, washed with toluene (20 ml) and dried to a temperature of 95-105^{O}C to afford the novel crystalline polymorph Form–III of Losartan potassium.

(Weight: 19 grams, 95%)

DETAILED DESCRIPTION OF THE ACCOMPANYING DRAWINGS

Fig-1 is characteristic X-ray powder diffraction pattern of novel crystalline Form-III of Losartan potassium.

Vertical axis: Intensity (CPS); Horizontal axis: 2θ (degrees). The significant 2θ values (in degrees) obtained are 7.154, 7.583, 8.042, 12.385, 13.233, 13.911, 15.267, 16.043, 17.194, 17.794, 18.483, 18.76, 19.293, 19.571, 20.728, 21.576, 24.192, 24.904, 25.695, 26.088, 27.773, 28.908, 29.474 and 30.614 two theta degrees.

Fig-2 is characteristic Differential Scanning Calorimetry thermogram of novel crystalline Form-III of Losartan potassium.

The Differential Scanning Calorimetry thermogram exhibits a major significant endo peak at 264.31°C.

Fig-3 is characteristic Infrared spectral data of novel crystalline Form-III of Losartan potassium.

The Infrared spectrum exhibits the significant IR bands at about 580, 1460, 1422, 1358, 1257, 1112, 1075, 999, 754, 668 cm^{-1}.

We claim:

1. A novel crystalline Form-III of 2-butyl-4-chloro-1- [[2'-(1H-tetrazol-5-yl) [1,1'-biphenyl]-4-yl] methyl]-1H-imidazole-5-methanol potassium salt (Losartan potassium).
2. The novel crystalline Form-III of Losartan potassium of claim 1 having X-ray powder diffraction pattern with peaks at about 7.154, 7.583, 8.042, 12.385, 13.233,13.911,15.267,16.043,17.194, 17.794, 18.483, 18.76, 19.293, 19.571, 20.728, 21.576, 24.192, 24.904, 25.695, 26.088, 27.773, 28.908, 29.474 and 30.614 degrees two theta.
3. The novel crystalline Form-III of Losartan potassium of claim 2 having an X-ray powder diffraction pattern is substantially as depicted in Figure 1.
4. The novel crystalline Form-III of Losartan potassium of claim 1 having Differential Scanning Colorimetery thermogram which exhibits a major significant endo peak at 264.31°C.
5. The novel crystalline Form-III of Losartan potassium of claim 4 having characteristic Differential Scanning Colorimetry thermogram substantially as depicted in Figure 2.
6. The novel crystalline Form-III of Losartan potassium of claim 1 having characteristic Infrared spectra which exbits significant bands at 1580.44, 1460.11, 1422.12, 1358.02, 1257.29, 1112.69, 1075.72, 999.97, 754.97, 668.25 cm^{-1}.
7. The novel crystalline Form-III of Losartan potassium of claim 6 having characteristic Infrared spectrum substantially as depicted in Figure 3.

8. The novel crystalline Form-III of Losartan potassium of claim 1 having melting range of 254-260°C.

9. A process for preparing novel crystalline Form-III of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl) [1,1'-biphenyl]-4-yl] methyl]-1H-imidazole-5-methanol potassium salt (Losartan potassium) comprises of;

   a) refluxing the reaction solution of 2-n-Butyl-4-chloro-1- [(2'-(1-triphenylmethyl-1H-tetrazole-5-yl)-1,1'-biphenyl-4-yl) methyl] 1H-imidazole-5-methanol (trityl Losartan) in a mixture of aqueous solution of potassium hydroxide and C_1-C_4 straight or branched chain alcoholic solvents such as methanol, ethanol, isopropanol, n-butanol, iso-butanol and tertiary butanol, preferably methanol;

   b) distilling off the solvent from the reaction solution of step (a);

   c) cooling the reaction mass of step (b) to a temperature of 25-40^{O}C accompanied by addition of water;

   d) filtering the reaction mass of step (c);

   e) washing the filtrate obtained in step (d) with aromatic solvents such as benzene, xylene, toluene or ethyl benzene, preferably toluene;

   f) separating the layers from reaction solution of step (e) and accompanied by distilling the water from aqueous layer;

   g) azeotropic distillation of water traces from the reaction mass of step (f) using water immisible aromatic solvents such as benzene, xylene, toluene or ethyl benzene, preferably toluene;

h) dissolving the compound of step (g) in C_1-C_4 straight or branched chain alcoholic solvents such as methanol, ethanol, isopropanol, n-butanol, iso-butanol and tertiary butanol, preferably methanol;

i) optionally subjecting the reaction solution of step (h) with carbon;

j) optionally distilling the part of solvent from reaction solution of step (i) accompanied by cooling the resulting reaction mass to a temperature of 0-50^{O}C;

k) filtering the compound obtained in step (j) followed by drying the compound at temperature of 30-100^{O}C to afford the desired novel crystalline Form-III of Losartan potassium.

10. An another process for the preparation of crystalline Form-III of Losartan potassium, which comprises of;

a) heating the crystalline Form-I of Losartan potassium salt in water immisible aromatic solvents such as benzene, xylene, toluene or ethyl benzene, preferably toluene;

b) adding the C1-C4 straight or branched chain alcoholic solvents such as methanol, ethanol, isopropanol, n-butanol, iso-butanol and tertiary butanol, preferably methanol to the resulting reaction solution obtained in step (a);

c) distilling the part of solvent from the reaction solution of step (b) accompanied by cooling the reaction mass to a temperature of 10-50^{O}C, preferably 25-30^{O}C;

d) filtering the compound obtained in step (c) followed by drying the compound at a temperature of 30-100°C to afford the desired novel crystalline Form-III of Losartan potassium.

11. The process as claimed in claim 9 of step (a) where in the alcohol is methanol.

12. The process as claimed in claim 9 and 10 of step (a) where in the water immiscible aromatic solvent is toluene.

13. The process for the preparation of crystalline Form-III of Losartan potassium is substantially as herein described and exemplified.

Dated 23rd the day of July 2002

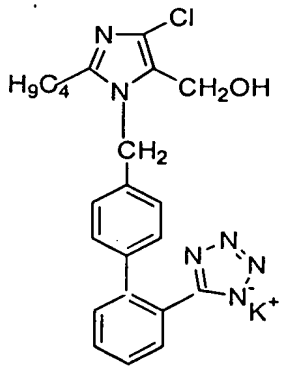
Signed)

Dr. Manne Satyanarayana Reddy,
Vice-President (R&D),
Dr. Reddy's Laboratories Limited.

ABSTRACT

Title of the invention: Novel Crystalline Form-III of 2-butyl-4-chloro-1- [[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl] methyl]-1H-imidazole-5-methanol potassium salt (Losartan potassium).

The present invention is directed to the novel crystalline Form-III of Losartan potassium, which is represented by Formula (1). The present invention also relates to the process for the preparation of novel crystalline Form-III of Losartan potassium, which involves treating Trityl Losartan with aqueous solution of potassium hydroxide in an alcoholic solvent such as methanol resulted the desired product and was isolated from a mixture of toluene and methanol.



Formula-1

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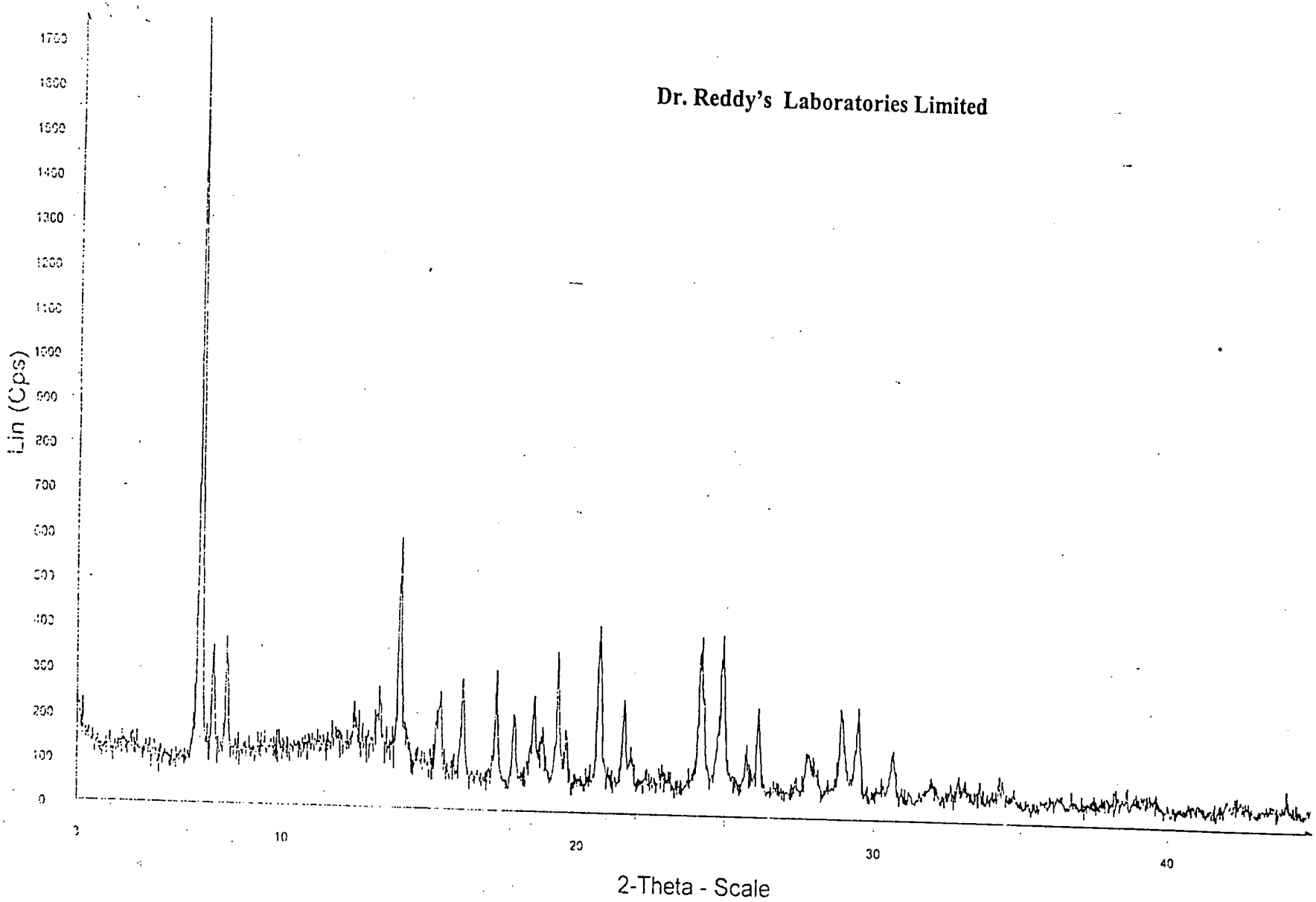
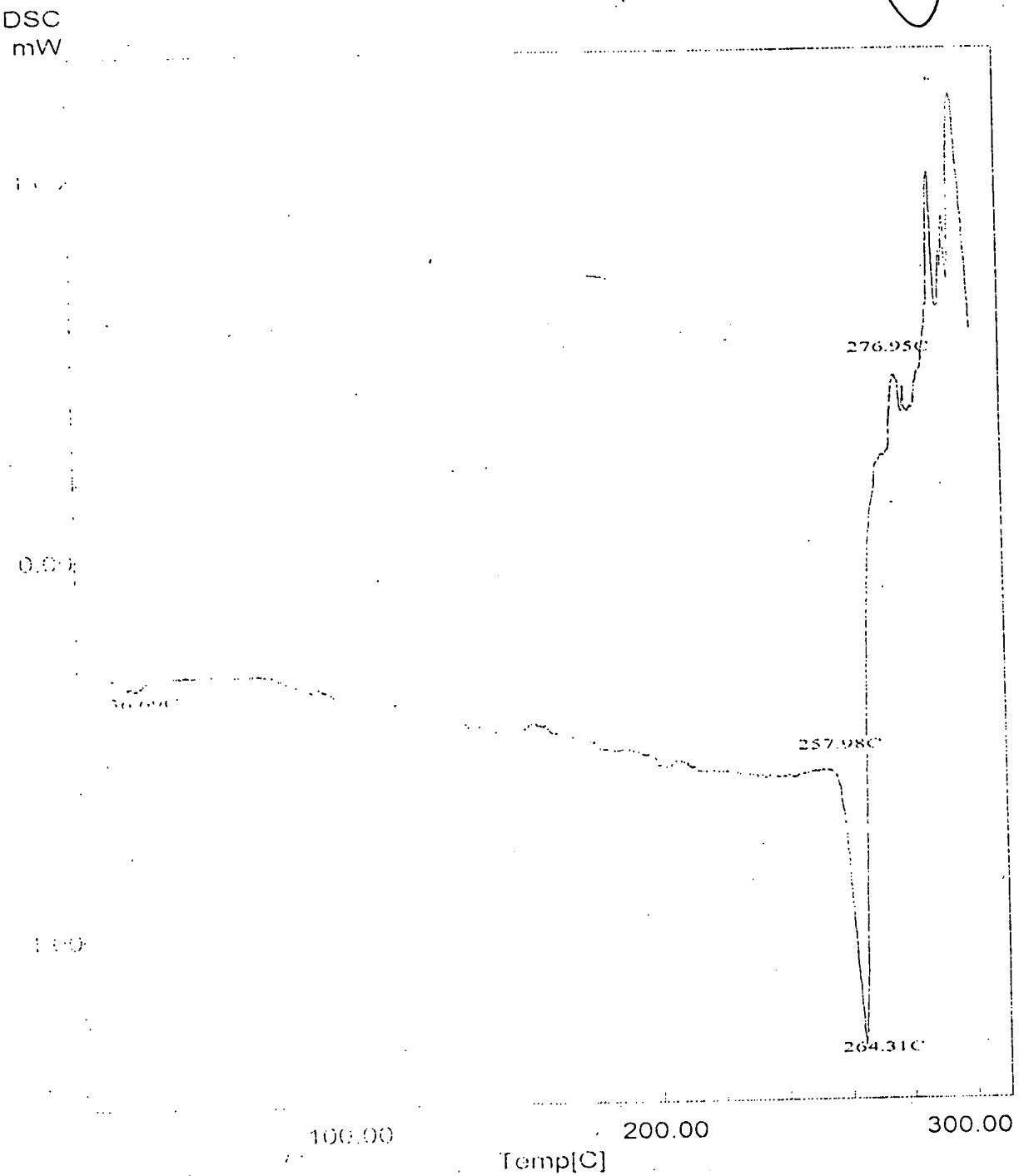


Fig. (1)

Thermal Analysis Data



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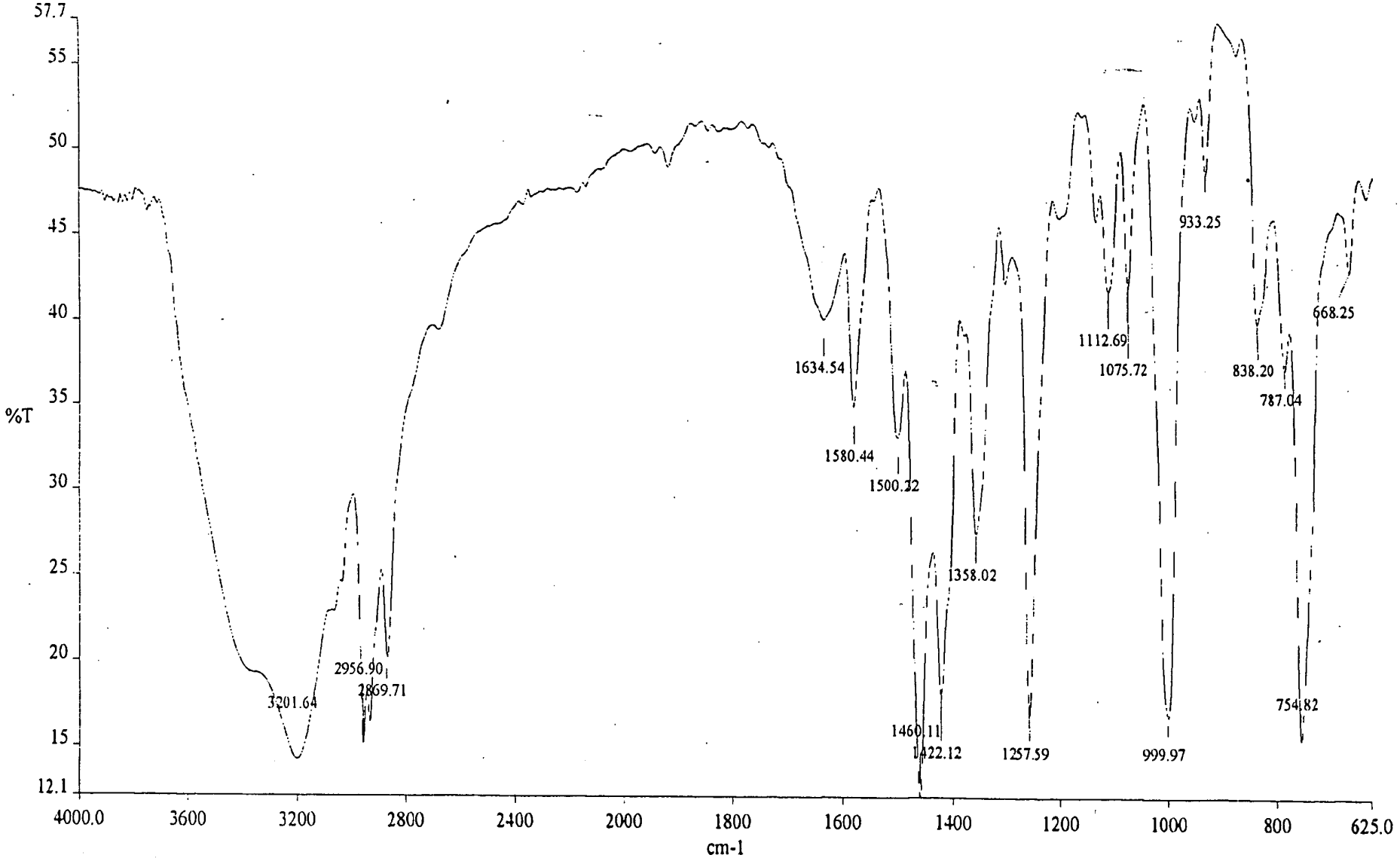

Fig.(3)